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INVITED EDITORIAL

Harmonizing hypercoagulable heterogeneity: Baseline VTE risk in COVID-19

Thrombosis in coronavirus disease 2019 (COVID-19) is a multifactorial process resulting from contributions of endotheliopathy, platelet activation, activation of the coagulation cascade, and derangement in the fibrinolytic systemic in the backdrop of immune dysregulation.[1-3] Venous thromboembolism (VTE), arterial thrombosis, and microvascular thrombosis have all been described in hospitalized patients with COVID-19, particularly during critical illness. Due to concerns about heightened thrombosis risks, the clinical practice at several treating institutions has been to incorporate escalated-intensity anticoagulation for some patients while awaiting clinical trials data on the safety and efficacy of this approach.[4-7]

An important and surprising limitation of the current literature is that thrombosis rates in different published reports of COVID-19–associated coagulopathy vary widely: Depending on the study, the reported prevalence of VTE in hospitalized patients with COVID-19 has been as low as 0% and as high as 85%.[8,9] This heterogeneity likely reflects key differences among individual studies in a number of factors. One is disease severity, as different studies have variably included critically ill, hospitalized noncritically ill, or ambulatory patients. The studies have also differed in their approach to imaging, with some employing screening imaging modalities in all patients and others using a nonscreening, symptom-directed approach. Different studies have included different types of thrombotic events, with the country of origin of each study and resultant use (or nonuse) of anticoagulant prophylaxis likely further impacting thrombosis rates in the various published reports.

In this issue of *Research and Practice in Thrombosis and Haemostasis*, Stephan Nopp and colleagues provide a comprehensive synthesis of data from all over the world on the risk of VTE in hospitalized patients with COVID-19, excluding studies with a high degree of bias.[10] In their meta-analysis, they analyzed a total of 28 173 patients from 66 studies originating in Europe, North America, and Asia, examining thrombosis rates in studies that incorporated either screening or nonscreening imaging. The overall VTE rates including both screening and nonscreening approaches were 22.7% (18.1%-27.6%) in the intensive care unit (ICU) setting and 7.9% (5.1%-11.2%) in the non-ICU setting. Among screening imaging studies in the ICU and non-ICU settings, VTE rates were 45.6% (30.6%-61.1%) and 23.0%; with a nonscreening approach, these were 18.7% (14.9%-22.9%) and 5.5% (3.6%-7.9%), respectively. In comparison to historical studies of patients without COVID-19, the compiled VTE rates in patients with COVID-19 in the ICU on pharmacologic thromboprophylaxis are higher, while the VTE risk in non-ICU patients is at least comparable.[11-13] This is particularly relevant considering that no major organization currently recommends more than prophylactic anticoagulation for hospitalized non-ICU patients with COVID-19, while the Anticoagulation Forum and the ISTH either endorse or allow for intermediate-dose anticoagulation in select patients who are critically ill.[5,7,14-16] Nopp and colleagues also analyzed VTE rates by study country of origin and found vast geographic variation, which the authors attributed to differences in individual study design, local practices regarding prophylactic anticoagulation, and inclusion of screening imaging for DVT.

One approach used by some institutions for hospitalized patients with COVID-19 is to customize risk stratification for VTE development with the use of D-dimer (DD) levels.[17] In their analysis of differences in baseline DD levels between patients with VTE and no VTE, Nopp and colleagues analyzed baseline DD from 21 studies that included 6633 patients and found an overall weighted mean difference in DD of 3.26 μg/mL (2.76-3.77) between patients who developed VTE and those who did not, acknowledging the variability in DD measurements globally. Additional risk factors that carry an increased risk of developing severe COVID-19 and traditionally carry a higher risk of thrombosis, such as advanced age, male sex, and obesity, could be used in a composite risk assessment for VTE development in COVID-19 and should be further examined in the context of clinical trials.

Given the increased risk of mortality with PE as opposed to DVT, known restrictions about computed tomography imaging for PE in the setting of COVID-19, and geographic variation in practices regarding prophylactic anticoagulation, accurate estimates of PE risk in hospitalized patients with COVID-19 are essential. By synthesizing these data and restricting the analysis to studies without a high degree of bias, the report by Nopp and colleagues represents a major advancement in the field. However, it is likely that the overall PE risks in their study are underestimated where clinical imaging restrictions are present. Periodic updates and reanalyses of these data will need to be undertaken, as data from clinical trials and other

higher-quality studies become available. On a societal level, cost effectiveness analyses of the varied anticoagulation practices implemented at different institutions and their impact on thrombosis, bleeding, and mortality rates will need to be explored, particularly in the subset of patients with COVID-19 who develop persistent aftereffects of this diagnosis. Understanding all of these factors will ideally enable clinicians to develop customized, case-by-case assessments of efficacy and safety of increased-intensity anticoagulation in the prevention of VTE in hospitalized patients with COVID-19.

AUTHOR CONTRIBUTIONS

GG and AIL wrote and edited the invited editorial commentary.

RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

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